

**WHAT IS CLAIMED IS:**

- 1                   1.       A method of inducing apoptosis in a cancer cell, the method  
2 comprising contacting the cell with:
  - 3                   i.       an anti-DR4 or anti-DR5 affinity agent agonist; and
  - 4                   ii.       an apoptosis-inducing agent.
- 1                   2.       The method of claim 1, wherein the agonist is an anti-DR-5 antibody.
- 1                   3.       The method of claim 2, wherein the anti-DR5 antibody has the binding  
2 specificity of an antibody comprising a heavy chain variable region comprising the sequence  
3 displayed in Figure 24 or Figure 35 and a light chain variable region as displayed in Figure  
4 25 or Figure 35.
- 1                   4.       The method of claim 3, wherein the anti-DR5 antibody comprises a  
2 heavy chain variable region comprising the sequence displayed in Figure 24 or Figure 35 and  
3 a light chain variable region as displayed in Figure 25 or Figure 35.
- 1                   5.       The method of claim 2, wherein the anti-DR5 antibody is Antibody A  
2 (ATCC Deposit No. \_\_\_\_).
- ✓ 1                  6.       The method of claim 1, wherein the agonist is an anti-DR4 antibody.
- 1                   7.       The method of claim 1, wherein the cell is contacted with an anti-DR4  
2 antibody agonist and an anti-DR5 antibody agonist.
- 1                   8.       The method of claim 1, wherein the agonist is a humanized antibody.
- 1                   9.       The method of claim 1, wherein the agonist is a single chain antibody.
- 1                   10.      The method of claim 1, wherein the agent prevents or reduces the  
2 expression of BCL-2.
- 1                   11.      The method of claim 10, wherein the agent prevents activation of  
2 NFκB.
- 1                   12.      The method of claim 11, wherein the agent prevents degradation of  
2 IκB.

- 1                    13.     The method of claim 1, wherein the agent is a proteasome inhibitor.
- 1                    14.     The method of claim 13, wherein the proteasome inhibitor is selected  
2 from the group consisting of PS-341, MG-262 and MG-132.
- 1                    15.     The method of claim 1, wherein the agent is an inhibitor of an Inhibitor  
2 of Apoptosis (IAP) protein.
- 1                    16.     The method of claim 15, wherein the inhibitor is SMAC or a SMAC  
2 mimetic.
- 1                    17.     The method of claim 1, wherein the cancer cell is a colon cancer cell or  
2 a pancreatic cancer cell.
- 1                    18.     The method of claim 1, wherein the agent is an antagonist of PAK1.
- 1                    19.     The method of claim 1, wherein the agent is an antagonist of a  
2 polypeptide selected from the group consisting of nsurf and JIK.
- 1                    20.     The method of claim 1, wherein the agent is a siRNA.
- 1                    21.     A method of inducing apoptosis in a cancer cell in an individual in  
2 need thereof, the method comprising,  
3 administering to the individual a therapeutically effective amount of  
4 i.       an anti-DR4 or anti-DR5 affinity agent agonist; and  
5 ii.      an apoptosis-inducing agent.
- 1                    22.     The method of claim 21, wherein the agonist and the agent are  
2 administered separately.
- 1                    23.     The method of claim 21, wherein the agonist and the agent are  
2 administered as a mixture.
- 1                    24.     The method of claim 21, wherein the agonist is an anti-DR-5 antibody.
- 1                    25.     The method of claim 24, wherein the anti-DR5 antibody has the  
2 binding specificity of an antibody comprising a heavy chain variable region comprising the

3 sequence displayed in Figure 24 or Figure 35 and a light chain variable region as displayed in  
4 Figure 25 or Figure 35.

1 26. The method of claim 25, wherein the anti-DR5 antibody comprises a  
2 heavy chain variable region comprising the sequence displayed in Figure 24 or Figure 35 and  
3 a light chain variable region as displayed in Figure 25 or Figure 35.

1 27. The method of claim 25, wherein the anti-DR5 antibody is Antibody A  
2 (ATCC Deposit No. \_\_\_\_\_).

1 28. The method of claim 21, wherein the agonist is an anti-DR4 antibody.

1 29. The method of claim 21, wherein the cell is contacted with an anti-  
2 DR4 antibody agonist and an anti-DR5 antibody agonist.

1 30. The method of claim 21, wherein the agonist is a humanized antibody.

1 31. The method of claim 21, wherein the agonist is a single chain antibody.

1 32. The method of claim 21, wherein the agent prevents or reduces the  
2 expression of BCL-2 or Ubch10.

1 33. The method of claim 32, wherein the agent prevents activation of  
2 NF $\kappa$ B.

1 34. The method of claim 33, wherein the agent prevents degradation of  
2 I $\kappa$ B.

1 35. The method of claim 21, wherein the agent is a proteasome inhibitor.

1 36. The method of claim 35, wherein the proteasome inhibitor is selected  
2 from the group consisting of PS-341, MG-262 and MG-132.

1 37. The method of claim 21, wherein the agent is an inhibitor of an  
2 Inhibitor of Apoptosis (IAP) protein.

1 38. The method of claim 37, wherein the inhibitor is SMAC or a SMAC  
2 mimetic.

1                   39.     The method of claim 21, wherein the cancer cell is a colon cancer cell  
2     or a pancreatic cancer cell.

1                   40.     The method of claim 21, wherein the agent is an antagonist of PAK1.

1                   41.     The method of claim 21, wherein the agent is an antagonist of a  
2     polypeptide selected from the group consisting of Ubch10, nsurf and JIK.

1                   42.     The method of claim 21, wherein the agent is a siRNA.

1                   43.     A physiological composition comprising, a therapeutically effective  
2     amount of

- 3                   i.        an anti-DR4 or anti-DR5 affinity agent agonist; and  
4                   ii.       an apoptosis-inducing agent.

1                   44.     The physiological composition of claim 43, wherein the agonist is an  
2     anti-DR-5 antibody.

1                   45.     The physiological composition of claim 44, wherein the anti-DR5  
2     antibody has the binding specificity of an antibody comprising a heavy chain variable region  
3     comprising the sequence displayed in Figure 24 or Figure 35 and a light chain variable region  
4     as displayed in Figure 25 or Figure 35.

1                   46.     The physiological composition of claim 45, wherein the anti-DR5  
2     antibody comprises a heavy chain variable region comprising the sequence displayed in  
3     Figure 24 or Figure 35 and a light chain variable region as displayed in Figure 25 or Figure  
4     35.

1                   47.     The physiological composition of claim 46, wherein the anti-DR5  
2     antibody is Antibody A (ATCC Deposit No. \_\_\_\_).

1                   48.     The physiological composition of claim 43, wherein the agonist is an  
2     anti-DR4 antibody.

1                   49.     The physiological composition of claim 43, wherein the cell is  
2     contacted with an anti-DR4 antibody agonist and an anti-DR5 antibody agonist.

- 1                    50.     The physiological composition of claim 43, wherein the agonist is a  
2     humanized antibody.
- 1                    51.     The physiological composition of claim 43, wherein the agonist is a  
2     single chain antibody.
- 1                    52.     The physiological composition of claim 43, wherein the agent prevents  
2     or reduces the expression of BCL-2 or UbcH10.
- 1                    53.     The physiological composition of claim 52, wherein the agent prevents  
2     activation of NFκB.
- 1                    54.     The physiological composition of claim 53, wherein the agent prevents  
2     degradation of IκB.
- 1                    55.     The physiological composition of claim 43, wherein the agent is a  
2     proteasome inhibitor.
- 1                    56.     The physiological composition of claim 43, wherein the agent is an  
2     inhibitor of an Inhibitor of Apoptosis (IAP) protein.
- 1                    57.     The physiological composition of claim 56, wherein the inhibitor is  
2     SMAC or a SMAC mimetic.
- 1                    58.     The physiological composition of claim 43, wherein the agent is an  
2     antagonist of PAK1.
- 1                    59.     The physiological composition of claim 43, wherein the agent is an  
2     antagonist of a polypeptide selected from the group consisting of UbcH10, nsurf and JIK.
- 1                    60.     The physiological composition of claim 43, wherein the agent is a  
2     siRNA.
- 1                    61.     An affinity agent with the binding specificity of an antibody  
2     comprising a heavy chain variable region comprising the sequence displayed in Figure 24 or  
3     Figure 35 and a light chain variable region as displayed in Figure 25 or Figure 35.

1                    62.     The affinity agent of claim 62, which is an antibody comprising a  
2 heavy chain variable region comprising the sequence displayed in Figure 24 or Figure 35 and  
3 a light chain variable region as displayed in Figure 25 or Figure 35.

1                    63.     A cell that expresses the antibody of claim 62.

1                    64.     A method of inducing apoptosis in a cancer cell, the method  
2 comprising contacting the cell with an affinity agent with the binding specificity of an  
3 antibody comprising a heavy chain variable region comprising the sequence displayed in  
4 Figure 24 or Figure 35 and a light chain variable region as displayed in Figure 25 or Figure  
5 35.